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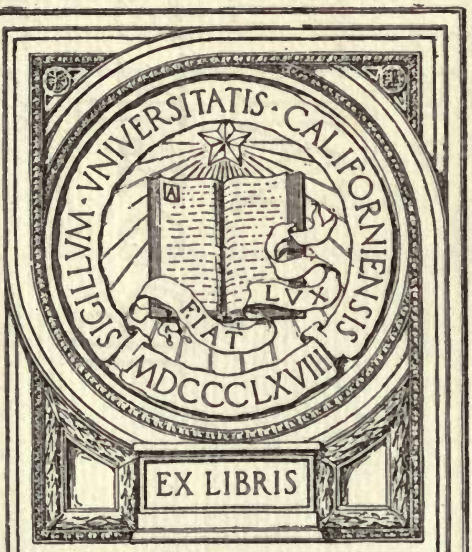

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EXCHANGE

Investigation in the Thiazole Field. The Synthesis of an Analog of Cinchophen

(ATOPHAN)

DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY

BY

EMANUEL M. ABRAHAMSON, B.S., Ch.E., M.A.

NEW YORK CITY

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UNIV. OF CALIFORNIA

QL 403 A2

TO THE MEMORY

OF

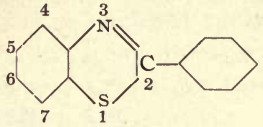
MY FATHER

ACKNOWLEDGMENT

The author desires to express his gratitude to Professor Marston Taylor Bogert, who suggested this work and under whose direction it was completed. Whatever merit this research may have is due to his kindly criticism, suggestions, and assistance.

ABSTRACT OF DISSERTATION.

Cyclicly bound sulfur has the effect of causing a marked rise in resorption, *i. e.* the reabsorption by the system of material previously separated out. A synthesis of a sulfur compound somewhat analogous, structurally, to α-phenyl cinchoninic acid was attempted in order to add the effect of nuclear sulfur to the uric acid solvent action of atophan. The compound prepared was 2-phenyl, benzothiazole carboxylic acid-6. It was made by nitrating μ-phenyl benzothiazole,



2 = μ.

reducing to the amine, and converting the latter into the acid by the Sandmeyer reaction.

The position of the amino group, and therefore of the carboxyl, was shown by the conversion of the amine into μ, μ′ -diphenyl benzobisthiazole, a compound previously synthesized from para-phenylene diamine.

The action of halogens on μ-phenyl benzothiazole was also studied. It forms an unstable tetrabrom addition product, which readily loses its bromine, the liberated bromine then substituting the 6-hydrogen to give a brom derivative which can also be obtained from the amine by the Gatterman reaction. The compound, on the other hand, adds but two atoms of iodine.

Curiously, it was found impossible to prepare an aldehyde or a ketone by the Gatterman-Koch or Friedel and Crafts reactions. These compounds would be interesting in that the effect of the odoriferous groups on the slightly fragrant μ-phenyl benzothiazole might produce a perfume.

In the course of this research the following compounds, hitherto unknown, were prepared:

6-amino, 2-phenyl benzothiazole*
6-benzylideneamino, 2-phenyl benzothiazole
6-acetamino, 2-phenyl benzothiazole
Para-nitro benzene-azo-6-amino, 2-phenyl benzothiazole
Para-nitro benzene-azo-6-acetamino,2-phenyl benzothiazole
μ-μ′-diphenyl benzobisthiazole†
Nitro, μ,μ′-diphenyl benzobisthiazole
Amino, μ,μ′-diphenyl benzobisthiazole
Acetamino, μ,μ′-diphenyl benzobisthiazole
6-dimethylamino, 2-phenyl benzothiazole
μ-phenyl benzothiazole tetrabromide
μ-phenyl benzothiazole di-iodide
6-brom, 2-phenyl benzothiazole‡
N-acetyl, chlor, 2-phenyl benzothiazole
2-phenyl benzothiazole carboxylic acid-6
Methyl ester of 2-phenyl benzothiazole carboxylic acid-6

* Previously prepared but not analyzed.

† Prepared previously but by an entirely different synthesis.

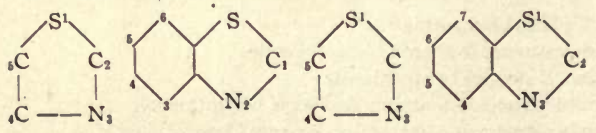
‡ Prepared in this work by two different methods.

INVESTIGATION IN THE THIAZOLE FIELD. THE SYNTHESIS OF AN ANALOG OF CINCHOPHEN (ATOPHAN)

Introductory

The Organic Laboratory of Columbia University has had under way for some time a number of investigations in the thiazole field, the results of which it hopes to publish as rapidly as opportunity permits.

The plan adopted for numbering the positions on the thiazole and benzothiazole nuclei both in Richter's "Lexikon" and in the Decennial Index to *Chemical Abstracts* is as indicated in Formulas I and II. This lack of uniformity seems to us highly undesirable and confusing. Therefore, we have employed consistently throughout this paper the numbering given in Formulas III and IV, so that S is always in position 1 and N at 3, while the C at 2 occupies the μ-, or middle position. This is in agreement with the system adopted in the new (2nd) edition of Meyer-Jacobson's "Lehrbuch der organischen Chemie.[1]"



I II III IV

For the experiments described in this first paper, 2-phenyl-benzothiazole has served as initial material, and from this interesting substance various derivatives have been prepared and studied.

Of the many methods of preparing this compound already given in the literature,[2] we have found fusion of benzanilide or benzalaniline

[1] Vol. II, Part 3, Sec. 2, pp. 535 and 549.

[2] *Ber.*, **10**, 2135 (1877); **12**, 2360 (1879); **13**, 8, 17, 1223, 1236 (1880); **15**, 2033 (1882); **19**, 1068, 1069 (1886); **23**, 2476 (1890); **35**, 1946 (1902); **44**, 3037 (1911); **48**, 1244, 1251 (1915). *Ann.*, **259**, 301 (1890). *Am. Chem. J.*, **17**, 1401 (1895). Ger. pat. 51,172 and 55,222; *Friedländer*, **2**, 301, 302 (1891)

with sulfur the most satisfactory. This is the more economical and expeditious method, although the crude product is usually slightly colored.

Perhaps the most remarkable physical property of this thiazole, especially since it is an unoxidized sulfur compound, is its very agreeable odor, recalling that of tea roses or the rose geranium, so that it has been known also as "Rosenkörper." This odor has not been encountered in similar strength in any of its homologs or derivatives.

Our experiments have disclosed another peculiarity, namely, its failure to react, in solution in carbon disulfide, with aluminum chloride, so that neither the Friedel and Crafts nor Gattermann-Koch reaction is available for the production of derivatives. In both cases, the thiazole is recovered practically unaltered. Further experiments are under way in this direction, however, as it has been shown in other cases that carbon disulfide occasionally inhibits these reactions.

It is difficult to understand Hofmann's statement[3] that fuming nitric acid is without action upon 2-phenyl-benzothiazole, for we have found that this compound is nitrated with the greatest ease by fuming nitric acid, as well as by a mixture of nitric and sulfuric acids, to give nearly theoretical yields of the nitro compound. Hofmann[3] did nitrate it with mixed acids and obtained the same nitro derivative as that described by us (m. p. 188°). His analysis showed it to be a mononitro derivative, but he did not determine the position of the nitro group. Naegeli[4] also nitrated the compound with mixed acids with similar results. He then fused this nitro derivative with potassium hydroxide and from the melt separated a substance, m. p. 234–6°, soluble in sodium carbonate solution which was re-precipitated by mineral acid and could be reduced by tin and hydrochloric acid to an amino compound. These and other properties seemed to agree with those of *p*-nitrobenzoic acid (m. p. 238°). He states that the results of the fusion were very unsatisfactory, the yield of *p*-nitrobenzoic acid being poor, and that there was extensive decomposition and carbonization. On the basis of this result, he assigned the nitro group a position in the 2-phenyl radical *para* to the μ-carbon of the thiazole nucleus. We have repeated Naegeli's experiments with the nitro compound, but were unable to isolate any crystalline products from the resultant tar.

Hofmann[3] noted that this nitro derivative could be readily reduced to a crystalline amine, whose hydrochloride was also crystalline[5] Remy, Erhart and Co. state that this hydrochloride is difficultly soluble. The patent covers the azo dyes made from the amine, although no data whatever are given concerning the amine itself, or the method of its

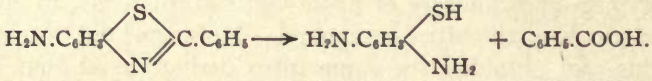
[3] Hofmann, *Ber.*, **13**, 1223 (1880).

[4] Naegeli, *Bull. soc. chim.*, [3] **11**, 895 (1894).

[5] Ger. pat., 57,557; *Friedländer*, **3**, 750 (1896).

preparation. We have found that reduction with tin and hydrochloric acid occurs smoothly and that the pure amine melts at 207° (corr.), whereas French patent 216,086[6] gives the melting point of *p*-aminophenyl-benzothiazole as 154–155°. There does not seem to be much doubt concerning the structure of the latter amine, since it was prepared by fusion of a mixture of aniline, *p*-toluidine and sulfur at 180–250°; and its use for the manufacture of azo dyes was also patented.[7] It has also been shown that the nitration of amino benzothiazoles gives nitro derivatives with the nitro group in the benzothiazole benzene nucleus, and not in the 2-phenyl radical.[8]

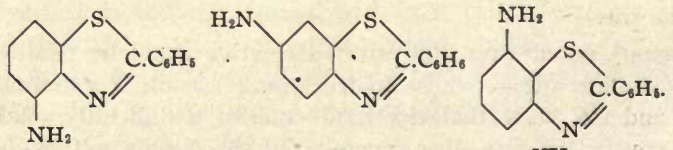
It appeared most unlikely, therefore, that direct nitration of 2-phenyl-benzothiazole would yield a derivative with its nitro group in the 2-phenyl nucleus. To prove the point, the amine was fused with caustic alkali, a reaction which proceeds much more smoothly than that with the corresponding nitro derivative. Benzoic acid itself was separated as the main product of this fusion. It follows from this that the amino group, and consequently the nitro group, must have been on the benzothiazole nucleus and not on the 2-phenyl nucleus.



A single attempt to isolate and identify the diamino-thiophenol, which should be the other main product of the fusion, was unsuccessful, and no further efforts were made, since the absence of any aminobenzoic was demonstrated, and this was deemed sufficient proof of the position of the nitro group.

As 5-amino-2-phenyl-benzothiazole has been described already,[9] and is not identical with the amine in question, the remaining possibilities are the 4-, 6- or 7-amino derivatives. The following experimental work led to a choice among these possibilities.

It has been observed frequently that an aromatic amine with free *para* and *ortho* positions, when treated with a diazonium salt under proper conditions, will couple twice, first in the *para* and then in the *ortho* position. Thus the 4- or 7-amino compound (V and VII) should couple twice, and the 6-amino derivative (VI) but once,



V VI VII

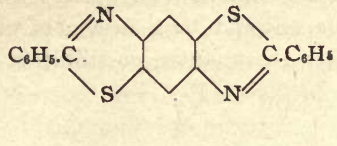
[6] *Winther*, **3**, 379 (1910).

[7] Ger. pat. 79,214; *Friedländer*, **4**, 829 (1899).

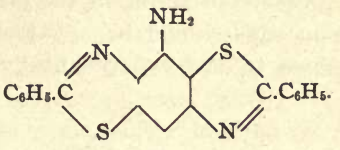
[8] Ger. pat. 81,711; *Friedländer*, **4**, 831 (1899).

[9] Kym, *Ber.*, **32**, 3534 (1899); Ger. pat. 75,674; *Friedländer*, **4**, 825 (1899).

With diazotized *p*-nitro-aniline, the new amine was found to couple but once. The conclusion that it was, therefore, the 6-amino derivative was further corroborated by converting it into its benzal derivative and fusing the latter with sulfur, when a benzobisthiazole was obtained identical with that secured by Green and Perkin[10] from *p*-phenylenediamine dithiosulfonic acid and benzaldehyde, to which they assigned Formula VIII,



VIII



IX

This benzobisthiazole was also nitrated, the resulting nitro derivative reduced to the amine and the amine fused with caustic alkali. Only benzoic acid was isolated, and no aminobenzoic, thus locating the (nitro and) amino group on the middle benzene nucleus (IX).

No dinitro-2-phenyl derivatives were encountered in our experiments. Such compounds have been described, however,[11] and from them diamines (m. p. 192°, 208° and 255–256°) prepared, as well as azo dyes from the latter.[12]

6-Amino-2-phenyl-benzothiazole methylated under pressure with methyl alcohol and hydrochloric acid gave only the tertiary compound, but no quaternary salt. This reaction is being examined further, especially in its bearing upon the formation and tinctorial properties of the thioflavines.

By means of the Sandmeyer reaction, the amino compound was changed to the corresponding nitrile and the latter saponified to the acid (XIII).

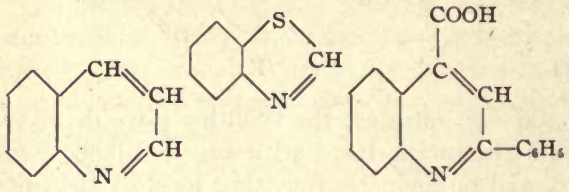
Quinoline is stated to have very powerful antiseptic, antipyretic and antizymotic action, but is too toxic and causes collapse. Sulfur in cyclic union, as in thiophene, ichthyol, etc., in addition to its antiseptic and antiparasitic properties, causes a marked increase in resorption, resembling iodine in this respect, although in no way similar to that, pharmacologically. Cyclic compounds containing substituted sulfur also show striking analgesic properties which can be ascribed only to the entry of sulfur into such groups. Quinoline, itself, a strong protoplasmic poison, on fusion with sulfur gives the so-called "thioquinanthrene," $NC_9H_5\langle{}^{S}_{S}\rangle C_9H_5N$, which is inert physiologically. In cyclic systems, one sulfur atom appears to

[10] Green and Perkin, *J. Chem. Soc.*, **83**, 1207 (1903).

[11] Ger. pat. 50,486; *Friedländer*, **2**, 303 (1891); and 54,921; *Friedländer*, **2**, 305 (1891).

[12] See also Ger. pat. 58,641; *Friedländer*, **3**, 765 (1896).

have much the same effect as an ethylene group, $-CH:CH-$, an analogy well illustrated by comparison of corresponding members of the benzene and thiophene series. The benzothiazoles (XI) are, therefore, the parallels to the quinolines (X), and show many striking points of similarity in their chemical behavior. Hence, the new acid noted above (XIII) may show some of the valuable properties of the well-known α-phenyl-cinchoninic acid (Cinchophen, or Atophan) (XII) as a remedy for gout. If the presence of sulfur in the complex should really prove to increase resorption, this should be a valuable adjunct to a uric acid eliminant. It is hoped to test experimentally its therapeutic possibilities.



X XI XII XIII

According to Ciusa and Luzzatto[13] most of the physiological action of 2-phenyl-cinchoninic acid is due to the 2-phenyl group, and this appears to be borne out by the fact that the following compounds show practically the same effect as cinchophen itself: its methyl or ethyl (Acitrin) esters, 6-methyl-2-phenyl-cinchoninic acid (Paratophan), the methyl (Novatophan K) or ethyl (Neocinchophen, Novatophan) esters of the latter, 8-methoxy-2-phenyl-cinchoninic acid (Isatophan), cinchophen salicylate, 2-phenylquinoline-4-diethyl carbinol, 2-phenyl-β-naphthoquinoline-γ-carboxylic acid (Diapurin), while cinchoninic acid, itself, is inactive. Modifications of the 2-phenyl group by substitution of H by OH, OR or NR_2 groups, seems to reduce the usefulness of the drug. The 2′-COOH derivative prepared by Reissert and Holle[14] in 1911 is therefore likely to show a different behavior physiologically from that of the isomer carrying the COOH group on the other benzene nucleus, even though the main function of this group is simply to render the complex more easily soluble. No record has been found of any physiological experiments with the product described by Reissert and Holle; it was not prepared with any such object in view, since it was merely incidental to a study of thiophthalanil.

In acetic acid solution, 2-phenyl-benzothiazole takes up 4 atoms of bromine per mole of thiazole; red crystals of the tetrabromo addition product $C_{13}H_9NSBr_4$ separate. This behavior parallels that of the analogous selenium compound, which also adds 4 bromine atoms. Fromm and

[13] Ciusa and Luzzatto, *Atti accad. Lincei*, [5] **22**, I, 305 (1913); *Gazz. chim. ital.*, **44**, I, 64 (1914); *Zentr.*, **1913**, II, 1318.

[14] Reissert and Holle, *Ber.*, **44**, 3035 (1911).

Martin[15] assigned the structure $C_6H_4\left\langle\begin{matrix}N(Br_2)\\ Se(Br_2)\end{matrix}\right\rangle C.C_6H_5$ to the product, basing this conclusion on the ease with which the bromine could be displaced and the parent selenazole regenerated. The bromine addition product of 2-phenyl-benzothiazole is less stable than the corresponding selenazole compound, since it loses bromine even on standing at ordinary temperature. This is in line with the lower basicity of sulfur. When heated in 2:1 acetic acid, the solution suddenly turns colorless and white crystals of a monobromo substitution product, $C_{13}H_8NSBr$, are deposited as the solution cools. This bromo derivative was proved to be the 6-bromo compound by preparing the same substance from the 6-amino derivative through the diazo reaction. This is similar to the transition of benzalaniline dibromide to benzal *p*-bromo-aniline and hydrochloric acid.[16]

Iodine also forms an unstable addition product with 2-phenyl-benzothiazole, from which sodium thiosulfate removes the halogen quantitatively, thus affording a convenient method of analysis. Unlike the analogous selenazole, only 2 atoms of iodine are added per mole of thiazole, instead of 4, a behavior also in harmony with the weaker basicity of sulfur. As this addition product contains about 50% of iodine by weight, it offers possibilities as an iodoform substitute, since it may combine the action of nuclear sulfur with that of the iodine.

Like quinoline, 2-phenyl-benzothiazole dissolved in toluene adds acetyl chloride readily; the product is decomposed immediately by water or on application of heat.

Other experimental work under way with this thiazole relates to its reduction, the behavior of the 6-amino derivative when subjected to such ordinary aniline reactions as lead to the corresponding quinoline, the cinchophen (Atophan) (*i. e.*, from the 6-benzalamino derivative and pyruvic acid), the phenol, various dyes, etc., and will be reported later.

Experimental Part

2-Phenyl-benzothiazole, $C_{13}H_9NS$.—(*a*). From Benzanilide.—The Hofmann process[3] was employed with a few modifications. Five hundred g. of benzanilide and 200 g. of sulfur (2.5 equivalents) were fused together at 250–260° until evolution of steam ceased. The melt was then distilled under diminished pressure from 2 Pyrex flasks with side tubes sealed together. The main distillate which came over at 220° at 19 mm. was cooled, pulverized and boiled for an hour under a reflux condenser with one liter of hot conc. hydrochloric acid. The yellow acid extract was filtered hot through asbestos, and the filtrate added to 6 liters of cold water. After the precipitated thiazole was crystallized from alcohol, it melted at 114° (corr.). Yield, 400 g. or 75%.

[15] Fromm and Martin, *Ann.*, **401**, 1781 (1913).

[16] Hantzsch, *Ber.*, **23**, 2774 (1890).

(*b*). From Benzalaniline.—This is also a modification of a method already in the literature.[17] Five hundred g. of benzalaniline, prepared by mixing equal moles of benzaldehyde and aniline and heating the mixture at 120–130° until all water was removed, was heated with 200 g. of sulfur (2.25 equivs.) at 250–260° until no more hydrogen sulfide was evolved, and the heating then continued for 2 hours longer under reduced pressure. The crude melt, purified as above, gave a yield of pure product (m. p. 114°) amounting to 375 g. or 64%. With either of the above methods, when the temperature rises much higher than that given the yield is diminished considerably. Distillation under diminished pressure is the quickest way to secure a colorless product, but is troublesome. The substance obtained by extracting the crude melt directly with hot conc. hydrochloric acid, when purified as indicated above, melts at practically the same point (114°), although it often has a pale yellowish cast. For most purposes, therefore, the undistilled product is entirely suitable.

The second method has been found to be the more rapid, economical and convenient, although the crude product from benzanilide is apt to be rather lighter in color.

6-Nitro-2-phenyl-benzothiazole, $C_{13}H_8NS(NO_2)$.—After 21 g. (0.1 mole) of the thiazole was added slowly to 150 cc. of fuming nitric acid (sp. gr. 1.60), the solution was allowed to stand for half an hour and then poured into 500 cc. of cold water. The precipitated nitro derivative was collected and crystallized from glacial acetic acid. M. p. 188° (corr.). Yield, 24 g., or 94%.

In another series of experiments we followed in the main the process of Naegeli.[4] Twenty one g. of the thiazole was dissolved in 100 cc. of conc. sulfuric acid. This solution was stirred and the temperature kept at 75° while a mixture of 15 g. (0.12 mole) of conc. nitric acid and 20 g. of conc. sulfuric acid was added drop by drop. The stirring was continued for half an hour after all of the nitric acid had been added. Then the mixture was heated at 100° for an hour, allowed to cool, poured into 1500 cc. of cold water, the precipitate collected and crystallized from glacial acetic acid as yellow needles, m. p. 188° (corr.); yield, 25 g., or 98%. Both Hofmann[3] and Naegeli[4] give the melting point as 188°.

Fusion of the Nitro Derivative with Caustic Alkali.—Ten g. of this nitro compound, 20 g. of potassium hydroxide and 40 g. of water, were heated together for 15 minutes at 200–210°. After cooling the solution, it was diluted, the tar removed and the filtrate acidified. A trace of colorless solid separated, insufficient to recrystallize or purify; it did not melt sharply but began to soften in the vicinity of 100°. Naegeli believed that he isolated *p*-nitrobenzoic acid (m. p. 238°) from this material but we failed to confirm this, although 4 times as much initial material was used by us.

6-Amino-2-phenyl-benzothiazole, $C_{13}H_8NS(NH_2)$, (Formula VI).—Twenty-five and six-tenths g. (0.1 mole) of nitro derivative and 40 g. (0.33 mole) of granular tin were covered with 150 cc. of conc. hydrochloric acid, and the flask warmed to start the reaction. The reduction proceeded with evolution of so much heat that it was necessary to chill the flask. On completion of the reduction the solution was allowed to cool and crystals of the double tin salt separated. The mixture was made strongly alkaline, the precipitated base collected, washed with 3 *N* sodium hydroxide solution (to remove tin salts) and then with water. The crude base, crystallized from aniline and finally from toluene, gave colorless needles, m. p. 207° (corr.); yield, 16 g. or 71%.

Analyses. Calc. for $C_{13}H_{10}N_2S$: N, 12.39. Found: 12.34, 12.43.

This amine is practically insoluble in water, in dilute acids, or in concentrated hydrochloric acid; difficultly soluble in methyl, in ethyl or in *iso*-amyl alcohol, ethyl or *iso*-amyl acetate, chloroform, carbon tetrachloride, benzene or toluene, and still more difficultly soluble in ether. Dilution with ether generally precipitates it from solution

[17] Ziegler, *Ber.*, **23**, 2476 (1890); Ger. pat. 51,172; *Friedländer*, **2**, 301 (1891).

in other solvents. Its alcoholic solutions show a beautiful blue fluorescence, and even ether takes up sufficient to show this fluorescence, too.

ACETYL DERIVATIVE.—From the base and acetic anhydride the acetyl derivative crystallizes in cubes, m. p. 214° (corr.).

Analyses. Calc. for $C_{15}H_{12}ON_2S$: N, 10.43. Found: 10.49, 10.57.

FUSION OF THE AMINE WITH CAUSTIC ALKALI.—Fifteen g. of amine and 60 g. of moist potassium hydroxide were fused for 15 minutes at as low a temperature as possible. The cool melt was dissolved in water, filtered, the filtrate acidified, and the precipitate crystallized from water. It melted at 122°, and was free from nitrogen and sulfur. Mixed with pure benzoic acid, the melting point remained unchanged. Some of it was dissolved in absolute alcohol, the solution saturated with dry hydrogen chloride, and water then added. Upon treatment with sodium carbonate solution, oily droplets separated which had the odor characteristic of ethyl benzoate.

p-Nitrobenzene-azo-(6-amino-2-phenyl-benzothiazole), $O_2N.C_6H_4.N:N.C_{13}H_7NS(NH_2)$.—Two and three-quarters g. of *p*-nitro-aniline was diazotized and the solution poured into a suspension of 4.5 g. of the aminothiazole in 100 cc. of 1:10 g. hydrochloric acid. The mixture was cooled and stirred for an hour; then the brown precipitate was collected, washed with water, crystallized from aniline, and the aniline removed by dil. hydrochloric acid. Red needles, melting at 196° (corr.) were obtained. They were difficultly soluble in aniline or in nitrobenzene, and practically insoluble in most other organic solvents; yield, 5 g., or 67%.

Analyses. Calc. for $C_{19}H_{13}O_2N_5S$: N, 18.67. Found: 18.70, 18.75.

ATTEMPTED FURTHER COUPLING.—Two and three-quarters g. of *p*-nitro-aniline was diazotized and allowed to act upon the amine as before. To this solution, an equal amount of diazotized *p*-nitro-aniline was added, while the temperature was kept below 5° and the mixture was stirred vigorously for half an hour. The brown precipitate obtained by the first coupling remained unchanged. The mixture was then filtered and the filtrate divided into two parts. The precipitate was washed thoroughly with water and crystallized from aniline, when it melted at 194–195° (corr.). Mixed with the product from the previous experiment, the melting point was 195°+ (corr.). One part of the filtrate from the brown precipitate was made alkaline, but no change was observed. The other portion was added to an alkaline solution of phenol, causing an immediate intense red color and the formation of an orange precipitate on acidification, which proved the presence of unaltered diazo-*p*-nitro-aniline. Hence, the original amine couples but once.

ACETYL DERIVATIVE.—This was obtained from the azo derivative and acetic anhydride as golden-yellow plates, m. p. 203° (corr.).

Analyses. Calc. for $C_{21}H_{15}O_3N_5S$: N, 16.01. Found: 16.01, 15.74.

6-Benzalamino-2-phenyl-benzothiazole, $C_6H_5.CH:N.C_{13}H_8NS$.—Twenty-two and six-tenths g. (0.1 mole) of aminothiazole was suspended in 150 cc. of alcohol, 15 cc. (0.15 mole) of benzaldehyde added and the mixture boiled gently for an hour; the solution boiled with bone black, filtered and cooled gave pale yellow plates, m. p. 151° (corr.); yield, 30 g., or 96%.

Analyses. Calc. for $C_{20}H_{14}N_2S$: N, 8.92. Found: 8.98, 8.81.

It is practically insoluble in water, and difficultly soluble in alcohol, ethyl or *iso*amyl acetate, ether, choroform, carbon tetrachloride, acetic acid, benzene or toluene.

2,2′-Diphenyl-benzobisthiazole (Formula VIII).—Twenty g. of this benzalamino derivative was fused with 10 g. (5 equivalents) of sulfur for 4 hours at 250–60°, and the heating then continued for an hour longer under diminished pressure. The cold melt was pulverized, and extracted repeatedly with hot conc. hydrochloric acid. The acid

extract (200 cc.) was poured into 1 liter of water, and the precipitate collected and crystallized from acetic acid giving pale yellow needles, m. p. 235° (corr.); yield, 7 g. or 32%.

Analyses. Calc. for $C_{20}H_{12}N_2S_2$: N, 8.14. Found: 8.08, 8.17.

Green and Perkin[10] prepared a diphenyl-benzobisthiazole, from *p*-phenylenediamine dithiosulfonic acid and benzaldehyde, which crystallized from amyl alcohol in pale straw colored needles, m. p. 232–4°, and which appears to be identical with the compound described above.

4-Nitro-2,2′-diphenyl-benzobisthiazole, $O_2N.C_{20}H_{11}N_2S_2$.—Five g. of the above bisthiazole was dissolved in 20 cc. of conc. sulfuric acid, 3 cc. of conc. nitric acid added slowly, the solution left at room temperature for half an hour, then heated at 100° for an hour, cooled, and poured into 200 cc. of ice water. The yellow precipitate was collected, crystallized from nitrobenzene, washed with methyl alcohol (to remove the solvent) and dried giving a yield of 4 g., or 70% of yellow needles, m. p. 262° (corr.). The substance is difficultly soluble or insoluble in methyl, ethyl or *iso*amyl alcohol, ethyl or *iso*amyl acetate, ether, acetic acid or anhydride, chloroform or carbon tetrachloride, benzene, toluene or xylene.

Analyses. Calc. for $C_{20}H_{11}O_2N_3S_2$: N, 10.80. Found: 10.93, 10.95

4-Amino-2,2′-diphenyl-benzobisthiazole was prepared by boiling 3 g. of the nitro compound for several hours with 3.5 g. of tin and 30 cc. of conc. hydrochloric acid, until the reduction was complete. The solution was made strongly alkaline with sodium hydroxide, the precipitated base collected on a filter, crystallized from aniline, the crystals were washed free from aniline by dil. hydrochloric acid, then washed with dil. ammonia and dried over conc. sulfuric acid. A yield of 2 g., or 72%, of yellowish needles was obtained; m. p. 285–287° (corr.).

Analyses Calc. for $C_{20}H_{13}N_3S_2$: N, 11.70. Found: 11.93, 11.98.

Acetyl Derivative.—This was obtained from the amine and acetic anhydride and forms colorless plates, m. p. 250–253° (corr.).

Analysis. Calc. for $C_{22}H_{15}ON_3S_2$: N, 10.47. Found: 10.62.

Fusion of the Amine with Caustic Alkali.—One g. of this amine was fused with 4 g. of moist potassium hydroxide at a low temperature for 10 minutes, the melt allowed to cool, dissolved in 25 cc. of water, filtered and the filtrate acidified with hydrochloric acid. The precipitate obtained was removed and crystallized from water. It proved to be benzoic acid (m. p. 122°). The filtrate was neutralized with ammonia, evaporated to dryness on the water-bath, the residue warmed with 5 cc. of acetic anhydride, the solution filtered through glass wool, and the filtrate carefully diluted. No acetamino-benzoic acid was obtained. Therefore the amino group must have been on the central benzene nucleus and not on either the 2- or 2′-phenyl nucleus.

6-Dimethylamino-2-phenyl-benzothiazole, $(CH_3)_2N.C_{13}H_8NS$.—Ten g. of 6-amino-2-phenyl-benzothiazole, 6 cc. of conc. hydrochloric acid and 20 cc. of absolute methyl alcohol were heated together in a sealed tube at 175° for 24 hours. The tube then contained a red viscous liquid which, on standing, deposited reddish-brown needles which were recrystallized from acetone and then melted at 185 (corr.); yield, 4 g., or 36%.

Analyses. Calc. for $C_{15}H_{14}N_2S$: N, 11.03. Found: 11.21, 11.11.

No methyl chloride addition product was found.

2-Phenyl-benzothiazole Tetrabromide, $C_{13}H_9NSBr_4$.—Ten g. of 2-phenyl-benzothiazole was dissolved in 250 cc. of acetic acid, 10 cc. of bromine (2 molec. equivalents) added, the mixture shaken vigorously for 10 minutes and allowed to stand for half an hour. Red needles separated which were collected and dried over potassium hydroxide

in vacuo. The compound is quite unstable, giving off bromine on standing. The crystals were therefore dried for only half an hour. The substance melted in the neighborhood of 125°, with considerable decomposition; yield, 15 g., or 60%.

Analyses. Calc. for $C_{13}H_9NSBr_4$: N, 2.64; Br, 60.22. Found N, 2.68, 2.80; Br. 59.95.

Bromine was determined by adding the sample to a very dilute sodium hydrogen sulfite solution, filtering out the liberated 2-phenyl-benzothiazole, acidifying the filtrate and precipitating the bromine ion as silver bromide.

6-Bromo-2-phenyl-benzothiazole, $Br.C_{13}H_8NS$.—In a subsequent experiment for the preparation of the above tetrabromide, the acetic acid solution of the thiazole (10 g.) and bromine (10 cc.) was diluted with 150 cc. of water and warmed to complete the solution. The effect of this dilution and warming, however, caused a sudden change in the course of the reaction; the red color of the solution disappeared, with evolution of bromine, and a colorless solid separated which crystallized in plates as the material cooled. These were recrystallized from acetic acid, and proved to be a monobromo substitution product, m. p. 152° (corr.); yield, 13 g., or 94%.

Analyses. Calc. for $C_{13}H_8NSBr$: C, 53.79; H, 2.78; N, 4.83; S, 11.05; Br, 27.55. Found: C, 54.44; H, 3.03; N, 4.79; S, 11.08; Br, 27.28.

The results of nitration led us to infer that the bromine also had entered Position 6 on the nucleus. In order to confirm this conclusion 11.3 g. (0.05 mole) of the 6 amino derivative was suspended in a mixture of 50 cc. of water and 10 cc. of conc. sulfuric acid at 0°, and 4 g. of sodium nitrite (0.05 mole) dissolved in 20 cc. of water added slowly while the mixture was cooled and stirred mechanically. When the diazotization was completed, 25 g. of potassium bromide was added and then (very slowly) 10 g. of copper powder. The ice-cold solution was gradually heated to boiling and kept at this temperature for half an hour; then it was cooled, the precipitated bromo derivative collected and crystallized twice from acetic acid, when it melted at 152° (corr.). Mixed with the compound obtained above from the tetrabromide, the melting point remained unaltered; yield, 3 g., or 21%.

Analysis. Calc. for $C_{13}H_8NSBr$: N, 4.83. Found: 4.89.

2-Phenyl-benzothiazole-di-iodide, $C_{13}H_9NSI_2$.—Twenty-one and one-tenth g. (0.1 mole) of 2-phenyl-benzothiazole was dissolved in acetic acid and a solution of 50.8 g. (0.2 mole) of iodine in the same solvent was added. The mixture was shaken for half an hour and then allowed to stand for several hours. A trace of crystalline material separated. An additional 21.1 g. of thiazole was then introduced. The solution soon deposited a large amount of glistening black needles, which were removed, washed with acetic acid, then with water, and dried over potassium hydroxide under diminished pressure, when they melted at 84.5° (corr.); yield, 78 g., or 85%.

Analyses. Calc. for $C_{13}H_9NSI_2$: I, 54.58. Found: 55.05, 54.98.

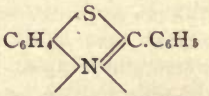
This addition product is quite unstable, and sodium thiosulfate removes its iodine quantitatively.

6-Cyano-2-phenyl-benzothiazole, $NC.C_{13}H_8NS$.—Fifty g. of cupric sulfate pentahydrate was dissolved in 100 cc. of warm water, a solution of 55 g. of potassium cyanide in 100 cc. of water was added, the mixture was heated to boiling and a suspension of the diazotized amine (prepared by adding a solution of 14 g. of sodium nitrite in 50 cc. of water to a suspension of 45.3 g. of amine in a mixture of 150 cc. of water and 50 cc. of hydrochloric acid and stirring for half an hour) added very slowly with active stirring. The mixture was boiled for half an hour longer, cooled and the precipitated nitrile collected. It is difficultly soluble or insoluble in ethyl or *iso*amyl alcohol or acetate, benzene, toluene or xylene, nitrobenzene, acetic acid, chloroform or carbon tetrachloride, and no good crystallizing medium was found for it.

2-Phenyl-benzothiazole-6-carboxylic Acid, (Formula XIII), $C_{13}H_8NS.COOH$.—The crude nitrile obtained above was boiled under a reflux condenser with a mixture of 100 cc. of conc. sulfuric acid and 60 cc. of water, until a test portion dissolved completely in dil. sodium hydroxide (about 15 hours). The solution was then cooled, poured into 2 liters of cold water and the precipitated acid removed. As no satisfactory neutral solvent could be found for crystallizing, it was dissolved in dil. sodium hydroxide and converted into the methyl ester by adding 50 g. (0.4 mole; twice the calculated amount) of dimethyl sulfate drop by drop, with simultaneous addition of sufficient dil. sodium hydroxide solution to keep the solution faintly alkaline. After stirring the mixture for an hour to insure destruction of all of the excess of dimethyl sulfate the separated thiazole methyl ester was filtered out, dissolved in alcohol, the solution boiled with bone black, and the ester crystallized to constant melting point, giving minute prisms of pale yellowish tinge, m. p. 153–154° (corr.); yield, 7 g., or 13%.

Analyses. Calc. for $C_{15}H_{11}O_2NS$: N, 5.20. Found: 5.11, 5.50.

This purified ester was saponified by boiling 6 g. of it with 200 cc. of 10% aqueous sodium hydroxide until all of it had dissolved. The hot solution was then boiled with bone black, filtered, the filtrate acidified with hydrochloric acid, the precipitated thiazole acid removed, washed and dried at 120° giving a slightly grayish powder, m. p. 261–263° (corr.) with decomposition; yield, 5 g., or 88% calculated to the ester, or 11% calculated back to the original amine.



Acetyl Chloride Addition Product of 2-Phenyl-benzothiazole, —On adding 5 g. of acetyl chloride to a solution of 5 g. of 2-phenyl-benzothiazole in 25 cc. of toluene, white leaflets of the addition product separated, amounting to 5 g. (73%). The substance lost the acetyl chloride very easily when it was warmed, so that the melting point obtained is that of the thiazole itself (114°).

It was analyzed by agitating it with water, filtering out the precipitated thiazole, and determining the chlorine in the filtrate with silver nitrate.

Analyses. Calc. for $C_{15}H_{12}ONSCl$: Cl, 12.24. Found: 11.98, 12.19.

Summary

1. An improved method is given for the preparation of 2-phenyl-benzothiazole in considerable quantities.

2. The product obtained by nitration of 2-phenyl-benzothiazole is shown to be the 6-nitro derivative by conversion, through the amine and its benzal derivative, into 2, 2′-diphenyl-benzobisthiazole. Hitherto the nitro group has been assigned position 4′ on the 2-phenyl nucleus.

3. The position of the amine group was further established by coupling it but once with diazotized *p*-nitro-aniline.

4. Nitro and amino derivatives of the 2,2′-diphenyl-benzobisthiazole were prepared and the positions of the groups determined.

5. 2-Phenyl-benzothiazole adds 4 bromine atoms directly. The tetrabromide lost bromine and hydrogen bromide when boiled with dil. acetic acid to form 6-bromo-2-phenyl-benzothiazole, which was also produced from the 6-amino derivative. With iodine, only 2 atoms are taken up; an unstable di-iodide results.

6. The addition product of 2-phenyl-benzothiazole and acetyl chloride loses acetyl chloride readily when heated or on treatment with water.

7. 6-Amino-2-phenyl-benzothiazole was changed into the cyanide, and the latter into the 6-carboxylic acid, which is structurally analogous to Cinchophen (Atophan), and which it is hoped may show useful therapeutic properties.

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VITA.

Emanuel M. Abrahamson was born in Brooklyn, N. Y., on June 25, 1897. After a preliminary education in the schools of that Borough he entered Columbia College in 1914, from which he received the degree of B. S. (*cum laude*) in 1917. He then studied Chemical Engineering in the School of Mines, Engineering and Chemistry of Columbia University, receiving the degree of Ch. E. in 1918. Upon his graduation, he entered the Chemical Warfare Service, U. S. A. and was stationed at Edgewood Arsenal. After his discharge from the army, he re-entered Columbia University to pursue studies under the Faculty of Pure Science. He was awarded the degree of M. A. in 1920. From 1918 to 1921 he held the position of assistant in the Department of Chemistry of Columbia University.

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